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Genetic Dissection Of Cognition In Humans And Mice Carrying Mutations

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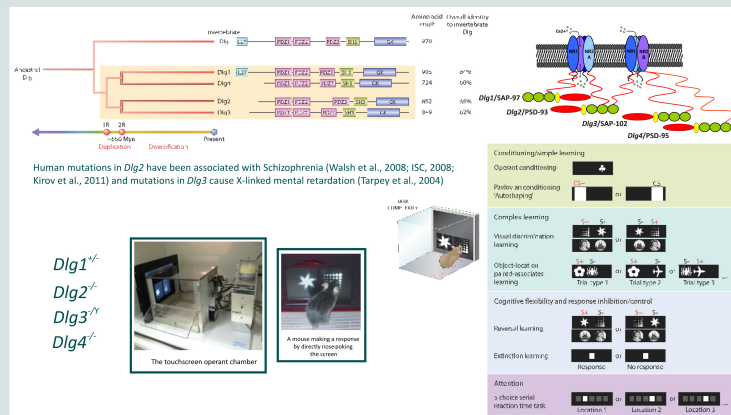
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INTRODUCTION

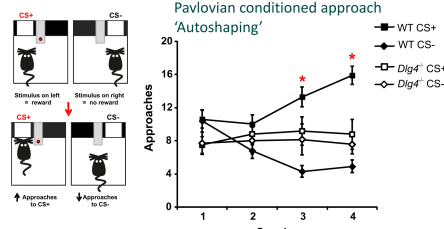
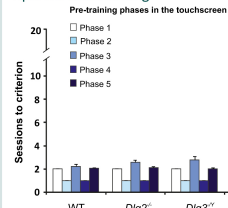
How the rich and diverse set of vertebrate higher cognitive functions and the susceptibility to human mental illness evolved is unknown. The vertebrate cognitive repertoire comprises multiple forms of learning, attention and executive functions, which are selectively disrupted in mental disorders, such as schizophrenia, autism and intellectual disability. Two whole genome duplications at the base of the vertebrate lineage generated gene paralogs that expanded and diversified the molecular complexity of simpler invertebrate synapse proteomes.



Dlg4 is essential for simple forms of conditioning and associative learning

Simple forms of learning

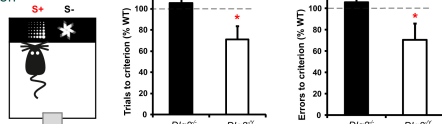
Operant conditioning



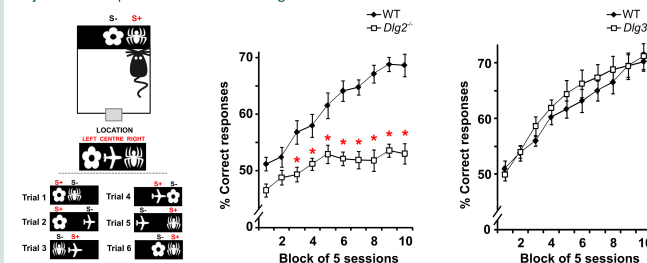
***Dlg2* and *Dlg3* play differential and opposing roles in complex forms of learning and information processing**

More complex forms of learning

Visual discrimination

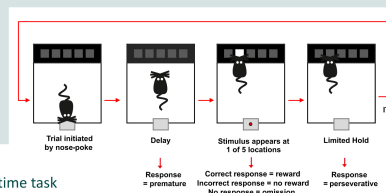
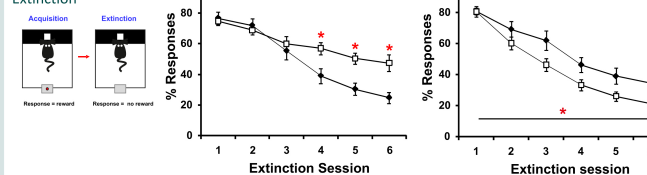


Object-location paired associates learning



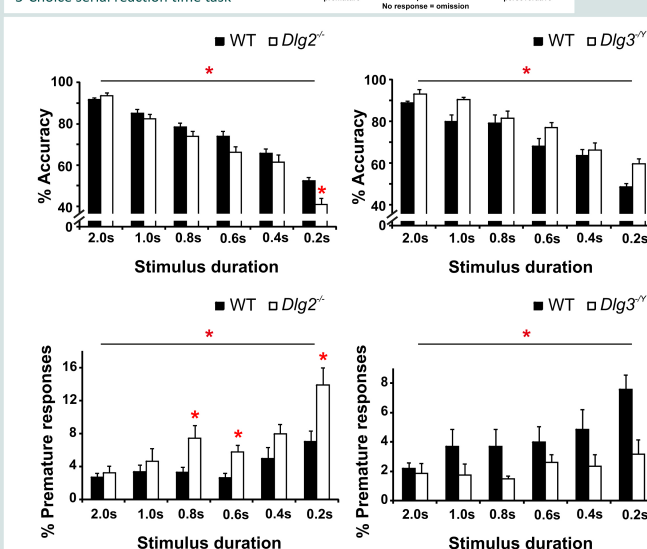
Response inhibition

Extinction



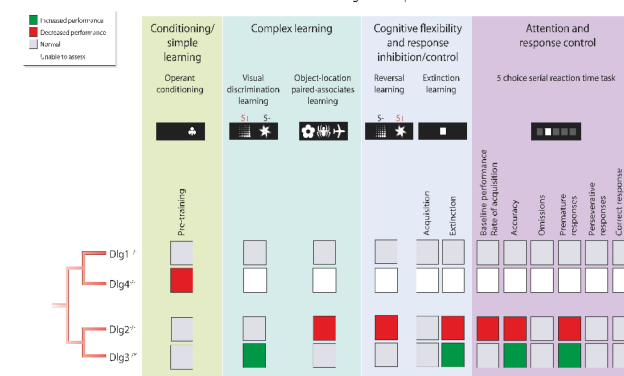
Attention

5-Choice serial reaction time task

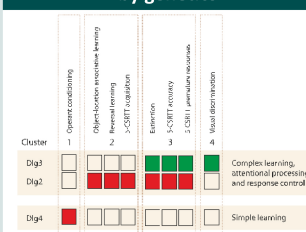


Paralog diversification and cognitive complexity

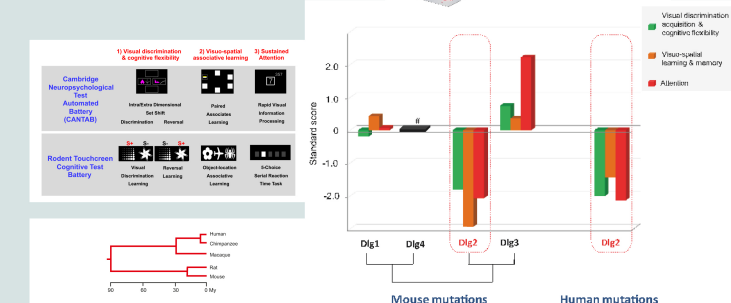
Cognitive repertoire



Clustering of cognitive functions by genetics



Conserved cognitive functions of *Dlg2* in humans



CONCLUSIONS

Our data demonstrate that paralogous gene duplication and diversification initiated over 500 million years (My) ago diversified the regulation of vertebrate higher cognitive functions and that the constraint in structure and function of these genes within the last 100 My conserved the specific cognitive roles of genes. While vertebrate expansion in Dlg and other postsynaptic gene families endowed vertebrates with an expanded and flexible set of cognitive functions, these benefits appear to have come at the price of increased susceptibility to mental illness.